REPORT DOCUMENTATION PAGE

AFOSR-TR-96 0132 97

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
		FINAL 30 Sep 93 TO 29 Sep 96

4. TITLE AND SUBTITLE

STRESS-INDUCED ENHANCEMENT OF THE STARTLE REFLEX

5. FUNDING NUMBERS

F49620-93-1-0293
61102F
2312/BS

6. AUTHOR(S)

Dr Michael Davis

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Dept of Psychiatry
Yale University School of Medicine
Abraham Ribicoff Research Facilities
Connecticut Mental Health Center
34 Park Street
New Haven CT 06508

8. PERFORMING ORGANIZATION REPORT NUMBER

9 SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

AFOSR/NL
110 Duncan Ave Suite B115
Bolling AFB DC 20332-8080

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

Dr Genevieve M. Haddad

11. SUPPLEMENTARY NOTES

19970314 053

12a DISTRIBUTION AVAILABILITY STATEMENT

Approved for public release;
distribution unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

A major goal of the work funded by the Air Firce over the previous grant periods was to evaluate the role of the amygdala in both conditioned and unconditioned fear and anxiety. During the last funding period, covered in the current Final Technical Report, we have investigated the role of a brain area closely associated with the amygdala, namely the bed nucleus of teh stria terminalis (BNST), in fear and anxiety, as well as in the anxiety producing effects of teh peptide, corticotropin releasing hormone. In addition, we have obtained further evidence concerning the neural pathway that mediates the primary accoustic startle reflex, changes in which we use as our marker of conditioned fear.

14. SUBJECT TERMS	15. NUMBER OF PAGES
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
(U)	(U)	(U)	(U)

Fax Transmission

Date: 2/21/97

To: MARILYN McKee
AF Office of Scientific Res

From: Dr MICHAEL DAVIS

Yale University School of Medicine
Abraham Ribicoff Research Facilities
Department of Psychiatry
Connecticut Mental Health Center
34 Park Street
New Haven, CT 06508

Telephone#: (203)-789-3450

Fax#: (203)-562-7079

No. of pages including cover page: 14

Message:

Final technical Report
No. F49620-93-1-0293 P00002

Please call if you experience any transmission problems.

Final Technical Report
Number: F49620-93-1-0293 P00002
Title: Stress-Induced Enhancement of the Startle Reflex
PI: Michael Davis

A major goal of the work funded by the Air Force over the previous grant periods was to evaluate the role of the amygdala in both conditioned and unconditioned fear and anxiety. During the last funding period, covered in the current Final Technical Report, we have investigated the role of a brain area closely associated with the amygdala, namely the bed nucleus of the stria terminalis (BNST), in fear and anxiety, as well as in the anxiety producing effects of the peptide, corticotropin releasing hormone. In addition, we have obtained further evidence concerning the neural pathway that mediates the primary acoustic startle reflex, changes in which we use as our marker of conditioned fear.

A. The role of the amygdala and BNST in fear-potentiated startle using either explicit or context cues

As outlined in previous progress and final technical reports, our laboratory and others have shown that the amygdala is critically involved in conditioned fear using explicit cues paired with aversive events. For example, if a light is paired with footshock and then the acoustic startle reflex is elicited in the presence of that light, the startle reflex is greater than when elicited by the same stimulus in the absence of the light (fear-potentiated startle). This is an example of fear conditioning using an explicit cue (i.e., the light). This effect is completely blocked by electrolytic or chemical lesions of the amygdala. Recently, we have been testing a new hypothesis which suggests that the BNST may be importantly involved in contextual conditioning but not explicit cue conditioning, whereas the amygdala is involved in both. Different groups of rats each were given electrolytic or sham lesions of either the central nucleus of the amygdala or the BNST. One week later, rats were presented with ten startle stimuli every day for 22 days. These stimuli were followed by either two light-shock pairings and six fear-potentiated test trials or six fear-potentiated test trials followed by two light-shock pairings.

As expected, there was a gradual development of fear-potentiated startle over the 22 days. Fear-potentiated startle was completely blocked by lesions of the amygdala, but not by lesions of the BNST. Under these training conditions, there

was a gradual increase in startle amplitude elicited by the initial ten startle stimuli, before any lights or shocks were presented, which we consider a measure of contextual conditioning or perhaps long-term sensitization of startle. In this case, lesions of either the amygdala or the BNST blocked contextual conditioning or long-term sensitization. Taken together, these data show that lesions of the amygdala block both explicit cue and contextual conditioning, whereas lesions of the BNST block contextual conditioning, but not explicit cue conditioning.

B. The role of the BNST vs. the septum and amygdala and the BNST in CRH-enhanced startle

Intraventricular (ICV) infusion of CRH (0.1 - 1.0 μg) produces a pronounced, dose-dependent enhancement of the acoustic startle reflex in rats. This excitatory effect begins about 20-30 min after infusion, grows steadily over a 2-hr test period, and lasts at least 6 hrs (CRH-enhanced startle). Intraventricular infusion of the CRH antagonist a-helical CRH_{9-41} (ahCRH - 25 or 50 μg) blocked CRH-enhanced startle when infused 5 min prior to CRH. Administration of ganglionic blockers or prior adrenalectomy did not block the excitatory effect of CRH on startle, indicating a central site of action. CRH-enhanced startle also was reversed when ahCRH was given 90 min after infusion of CRH. This suggests that exogenously applied CRH remains in the brain for a very long time after administration or that CRH given exogenously initiates a process that results in a long-lasting activation of endogenous CRH. While lesions of the paraventricular nucleus of the hypothalamus had no effect on CRH-enhanced startle, bilateral electrolytic lesions of the central nucleus of the amygdala significantly attenuated CRH-enhanced startle. Even though lesions of the amygdala attenuated CRH-enhanced startle, local infusion of CRH into the amygdala did not significantly elevate startle. These data led to the suggestion that the amygdala is part of the neural circuitry required for CRH to elevate startle, but does not appear to be the primary receptor area where CRH acts.

More recently, we have found that electrolytic lesions of the medial septal area, but not the lateral septal area, completely block CRH-enhanced startle. However, NMDA induced lesions of the same area failed to block the excitatory effects of CRH on startle and local infusion of CRH into the medial septal area produced only about a 30% elevation in startle. In addition, NMDA-induced lesions of the lateral and basolateral nuclei of the amygdala or ibotenic acid-induced lesions of the central nucleus of the amygdala failed to block CRH-enhanced startle. On the other hand, either electrolytic or chemical lesions of

the BNST did block the excitatory effect of CRH on startle. Hence, we now believe that electrolytic lesions of the medial septal area blocked CRH-enhanced startle by destruction of the fornix, which carries fibers projecting to the BNST. Moreover, the large size of the electrolytic lesions of the amygdala in the original study may also have damaged these fibers or caused degeneration of fibers into the BNST which somehow disrupted CRH-enhanced startle.

However, the interesting feature of these CRH results is that lesions that block contextual conditioning also block CRH-enhanced startle (e.g., lesions of the BNST), whereas lesions that block explicit cue conditioning do not (e.g., lesions of the amygdala). This suggests that CRH-enhanced startle and fear-potentiated startle are additive and hence may be independent. In fact, CRH given to rats trained in our usual fear-potentiated startle paradigm caused a significant increase in baseline startle but no effect on the magnitude of fear-potentiated startle, which shows simple additivity with CRH-enhanced startle. Moreover, in an extensive series of pilot studies, we have not found any blockade of fear-potentiated startle after ICV administration of (ahCRH), at doses that completely block CRH-enhanced startle. Interestingly, patients with post-traumatic stress disorder show very similar data in terms of baseline vs. fear-potentiated startle.

C. The light-enhanced startle effect

Although fear-potentiated startle offers several advantages as an animal model of fear and anxiety, one disadvantage, common to all procedures which rely upon conditioning, is that treatment effects cannot unambiguously be attributed to effects on fear vs memory. It is difficult to say, for example, whether a given drug which reduces fear-potentiated startle does so because the drug is anxiolytic or, alternatively, because the drug has a more general effect on memory retrieval. Consequently, it would be valuable to develop a procedure which preserves the benefits of fear-potentiated startle, but which relies upon unconditioned stimuli to elicit anxiety.

Previous reports suggest that bright light may be an anxiety provoking stimulus for rats and for mice. Recently, we have tested the effects of sustained illumination on the startle reflex and the possible role of the amygdala vs. the bed nucleus of the stria terminalis on the facilitatory effects of light on the startle reflex. Rats were exposed to 20 min. periods of darkness (Phase 1), removed from the test chambers, handled and then exposed for another 20 min to either darkness or bright light using either 8, 70, or 700 footlamberts of light (Phase 2) Throughout both test phases rats were presented with 105-db noise bursts every

30 sec. High levels of sustained illumination produced an increase in the amplitude of the acoustic startle response and the effect was directly related to the intensity of light during the second phase. This effect of light was blocked by systemic administration of the anxiolytic compound buspirone.

Recently, we have found that humans show a significant increase of startle amplitude (i.e., of the eyeblink response) in the dark. The opposite effects of illumination in rats vs humans may be attributable to the fact that rats are nocturnal whereas humans are diurnal. Interestingly, dark-enhanced startle only occurred in those subjects who rated the experiment as more unpleasant in the dark than in the light, and was correlated with the subjects' self-ratings of how fearful of the dark when they were young. Again, these results are consistent with the view that the effects of light on startle are related to fear or anxiety.

D. Effects of glutamate antagonists infused into the bed nucleus of the stria terminalis vs. the amygdala on light-enhanced startle

Because local infusion of glutamate antagonists into the central nucleus of the amygdala completely blocks the expression of fear-potentiated startle, we wondered whether this treatment would also block light-enhanced startle. As a control, we measured the effects of local infusion of glutamate antagonists into the bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis is considered to be part of the so-called extended amygdala because it is highly similar to the central nucleus of the amygdala in terms of its transmitter content, cell morphology and efferent connection However, lesions of the bed nucleus of the stria terminalis fail to block either fear-potentiated startle or conditioned freezing using an explicit cue, suggesting that it may not be involved in explicit cue conditioning. As outlined above, lesions of the bed nucleus of the stria terminalis blocked long-term sensitization of the startle reflex as well as the excitatory effect of the peptide corticotropin releasing hormone on startle.

Animals were implanted with bilateral cannulas in either the bed nucleus of the stria terminalis, the basolateral complex of the amygdala (i.e., the lateral and basolateral nuclei), or the central nucleus of the amygdala. One week later animals were tested for light-enhanced startle using the procedures described above. Prior to being placed into the chamber during Phase II, half of the animals were infused with the AMPA/kainate antagonist 6-nitro-7-sulphamoylbenzo(f)quinoxaline-2-3-dione (NBQX - 3 μg/side) and the other half with it's vehicle, phosphate buffered saline (PBS). Two days later these

procedures were repeated except animals previously infused with NBQX were now infused with PBS and vice-versa.

Consistent with previous results in non-infused rats, light increased the amplitude of the startle reflex when animals were shifted from the darkened chamber in Phase I to the brightly illuminated chamber in Phase II after infusion of PBS into each of the three brain structures. Infusion of the glutamate antagonist NBQX into the central nucleus of the amygdala had no effect on light-enhanced startle. On the other hand, infusion of NBQX into either the lateral/basolateral amygdala complex or the bed nucleus of the stria terminalis significantly decreased light-enhanced startle.

These data strengthen the conclusion that the bed nucleus of the stria terminalis and the basolateral amygdala, which receives visual input and projects to the bed nucleus of the stria terminalis, are critically involved in light-enhanced startle whereas the central nucleus of the amygdala is not. It is, however, possible that the cannulas in the central nucleus of the amygdala were misplaced and that this accounted for the lack of an effect of inactivation of the central nucleus on light-enhanced startle. Previous studies have shown that local infusion into the central nucleus of the amygdala blocks the expression of fear-potentiated startle.

If the central nucleus implants in the present study were located properly, then infusion of NBQX into these animals should also block fear-potentiated startle. To evaluate this, the rats used in the light-enhanced startle experiment were trained and tested for fear-potentiated startle after infusion of NBQX into either the amygdala or bed nucleus of the stria terminalis. Consistent with previous results, infusion of the glutamate antagonist into the central nucleus of the amygdala completely blocked the expression of fear-potentiated startle. This was also true after an infusion of NBQX into the basolateral nucleus of the amygdala. In contrast, infusion of NBQX into the bed nucleus of the stria terminalis had no effect on fear-potentiated startle. These data indicate, therefore, that the location of the cannulas into the central nucleus of the amygdala was adequate to allow infusion of NBQX to totally block fear-potentiated startle. Hence, the ineffectiveness of NBQX infused into the central nucleus of the amygdala to block light-enhanced startle cannot be attributed to misplaced cannulas. Moreover, these data show a double dissociation between inactivation of glutamate receptors in the central nucleus of the amygdala vs. the bed nucleus of the stria terminalis in relationship to fear-potentiated vs. light-enhanced startle.

E. Differential roles of the amygdala vs. the bed nucleus of the stria terminalis in fear vs. anxiety

The series of experiments outlined above shows a clear distinction between the central nucleus of the amygdala and the bed nucleus of the stria terminalis in relationship to fear-potentiated startle versus CRH-enhanced and light-enhanced startle. Lesions or chemical inactivation of the central nucleus of the amygdala completely block the expression of fear-potentiated startle but have no effect whatsoever on either light-enhanced startle or CRH-enhanced startle. Conversely, lesions or chemical inactivation of the bed nucleus of the stria terminalis significantly attenuated either light-enhanced startle or CRH-enhanced startle without having any effect whatsoever on fear-potentiated startle. At the present time, it is still unclear why these two structures separate so completely in relationship to fear-potentiated startle versus light-enhanced and CRH-enhanced startle. It is especially interesting, for example, that the basolateral amygdala appears to be involved in light-enhanced startle, as well as fear-potentiated startle, but not in CRH-enhanced startle. Visual information is known to reach the bed nucleus of the stria terminalis via projections from the perirhinal cortex to the basolateral nucleus. Because light-enhanced startle eventually must depend on visual information getting to the bed nucleus of the stria terminalis, the ability of chemical inactivation of the basolateral nucleus of the amygdala to block light-enhanced startle may reflect interruption of visual information passing through the basolateral nucleus of the amygdala to the bed nucleus of the stria terminalis. On the other hand, chemical lesions of the basolateral nucleus of the amygdala did not block CRH-enhanced startle. This may make sense because CRH-enhanced startle would not require visual input to the bed nucleus of the stria terminalis and hence interruption of the visual pathway to the bed nucleus of the stria terminalis would not be expected to block CRH-enhanced startle. It should be emphasized that the very same light is used in both fear-potentiated test and the light-enhanced startle test. The only difference is that in fear-potentiated startle the light is previously paired with a shock and is presented for a brief period of time whereas in light-enhanced startle the light is not paired with a shock and is presented for a relatively long period of time. It is likely that the necessity of the central nucleus of the amygdala in fear-potentiated startle is dependent on prior classical fear conditioning because a great deal of data show that the amygdala is critically involved in both the acquisition and expression of stimulus associations. This does not seem to be the case for the bed nucleus of the stria terminalis because lesions of this structure fail to block changes in behavior produced by prior aversive conditioning. It is considerably less clear however, why sustained

activation of the central nucleus of the amygdala via a very bright light source does not seem to be involved in light-enhanced startle. Similarly, the prolonged increase of startle produced by intraventricular administration of CRH also did not seem to involve the amygdala but instead the bed nucleus of the stria terminalis. It is possible, therefore, that in addition to differences between the two structures as they relate to prior classical conditioning, differences in the ability of neural networks in the two areas to respond in a sustained way to sensory activation could also explain the differences between these two areas in fear-potentiated startle versus light-enhanced startle. For example, perhaps the amygdala is especially able to respond to the onset of an aversive stimulus but then rapidly adapts to such activation so as to be prepared for a subsequent presentation of another aversive stimulus. On the other hand, the bed nucleus of the stria terminalis may be arranged in such a way that networks within this nucleus can respond in a much more sustained way to aversive stimulation leading to long-lasting changes in various behavioral responses via projections from the bed nucleus of the stria terminalis to different target areas in the hypothalamus and brain stem. This could also explain why the bed nucleus is more prominently involved in the excitatory effects of CRH on startle compared to the central nucleus of the amygdala. That is, the long lasting behavioral effects of CRH given intraventricularly would require activation of a structure which could respond in a continuous fashion to receptor occupation by CRH compared to a structure which only could respond in a phasic way. In fact, it might make sense to have separate brain areas respond phasically and tonically to aversive stimulation so as to be able to register both the immediate onset of an aversive experience as well as its prolonged presence, while maintaining a system such as the amygdala to allow responding in a phasic way to another aversive stimulus. Otherwise, if the "fear system" were completely saturated, then a subsequent presentation of a threatening stimulus might not be fully processed, severely comprising survival of the organism.

We suggest, therefore, that the bed nucleus of the stria terminalis may be a system that responds to signals more akin to anxiety than those akin to fear, whereas the amygdala is clearly involved in fear and perhaps not as much in anxiety. Both these structures have very similar efferent connections to various hypothalamic and brainstem target areas known to be involved in specific signs and symptoms of fear and anxiety. Both receive highly processed sensory information from the basolateral nucleus of the amygdala and hence are in a position to respond to emotionally significant stimuli. CRH is known to be released during periods of stress or anxiety, some of which may come from CRH

containing neurons in the amygdala which project to the bed nucleus of the stria terminalis and act on CRH receptors in the bed nucleus of the stria terminalis. Thus, phasic activation of the amygdala by certain stressors could lead to a long-term activation of the bed nucleus of the stria terminalis via CRH. If so, then compounds that specifically block CRH receptors in the bed nucleus of the stria terminalis might be especially effective in the treatment of anxiety while leaving the fear response largely intact.

F. The primary acoustic startle pathway.

In 1982, our laboratory proposed that acoustic startle was mediated by four synapses; three in the brainstem (the ventral cochlear nucleus; an area just medial and ventral to the ventral nucleus of the lateral lemniscus, and the nucleus reticularis pontis caudalis) and one synapse onto motoneurons in the spinal cord . Electrolytic lesions of these nuclei eliminated acoustic startle and single pulse electrical stimulation of these nuclei elicited startle-like responses with a progressively shorter latency as the electrode was moved farther down the startle pathway.

Because electrolytic lesions of the area just medial and ventral to the ventral nucleus of the lateral lemniscus eliminated the acoustic startle reflex, we concluded that this area must be part of a primary acoustic startle pathway. When we did the initial lesion work on this project, techniques were not yet available to selectively destroy cells vs. cells plus fibers passing through the area of the lesion. Using newly developed techniques to accomplish this, we found that N-methyl-D-aspartate (NMDA)-induced lesions of the ventral nucleus of the lateral lemniscus or the area just ventral and medial to it did not affect startle, whereas NMDA-induced lesions of cell bodies in the nucleus reticularis pontis caudalis completely eliminated startle.

These new data questioned the importance of the area around the ventral nucleus of the lateral lemniscus in mediating the acoustic startle reflex, even though this area is known to receive direct auditory input. On the other hand, all data still supported the critical importance of the nucleus reticularis pontis caudalis in the acoustic startle reflex. However, until very recently, it has been unclear how auditory information gets to this traditionally non-auditory part of the brainstem. It is now know that a same group of cells embedded in the cochlear nerve, termed cochlear root neurons, send thick axons through the trapezoid body directly to an area just medial and ventral to the lateral lemniscus and continue on up to the deep layers of the superior colliculus. However, they

give off thick axon collaterals which terminate directly in the nucleus reticularis pontis caudalis onto cells which then project to motoneurons in the spinal cord and brain stem.

We have now found that bilateral kainic acid-induced lesions of the cochlear root neurons essentially eliminated both whole body acoustic startle and the pinna reflex in rats. Although damage to the auditory root, where the cochlear root neurons reside, has not been fully ruled out, other tests indicated that these animals could clearly orient to auditory stimuli (e.g. suppression of licking) and had normal compound action potentials recorded from the cochlear nucleus .

Hence, we now believe that the acoustic startle pathway may be simpler than we had originally thought, consisting of only three synapses onto 1) cochlear root neurons; 2) neurons in the nucleus reticularis pontis caudalis and 3) motoneurons in the facial motor nucleus (pinna reflex) or spinal cord (whole body startle).

G. Publications:

Original articles

Rosen, J.B., Hitchcock, J.M., Miserendino, M.J.D., Falls, W A., Campeau, S. and Davis, M. Lesions of the perirhinal cortex, but not of the frontal, medial pre-frontal, visual or insular cortex block fear-potentiated startle using a visual conditioned stimulus. Journal of Neuroscience, 1992, 12, 4624-4633.

Morgan, C.A., Southwick, S.M., Grillon, C., Davis, M., Krystal, J.H. and Charney, D.S. Yohimbine facilitated acoustic startle reflex in humans. Psychopharmacology, 1993, 110, 342-346.

Kim, M., Campeau, S,. Falls, W.A., and Davis, M. Intra-amygdala infusions of the non-NMDA receptor antagonist CNQX blocks the expression of fear-potentiated startle. Behavioral and Neural Biology, 1993, 59, 5-8.

Grillon, C., Ameli, R,. Foot, M. & Davis, M. Fear-potentiated startle: Relationship to the level of state/trait anxiety in healthy subjects. Biological Psychiatry, 1993, 33, 566-574.

Kim, M. & Davis, M. Electrolytic lesions of the amygdala block acquisition and expression of fear-potentiated startle even with extensive training, but do not

prevent re-acquisition. Behavioral Neuroscience, 1993, 107, 580-595.

Grillon, C., Ameli, R., Woods, S.W. and Davis, M. Measuring the time course of anticipatory anxiety using the fear-potentiated startle reflex. Psychophysiology, 1993, 30, 430-346.

Falls, W.A. and Davis, M. Visual cortex ablations do not prevent extinction of fear-potentiated startle using a visual conditioned stimulus. Behavioral and Neural Biology, 1993, 60, 259-270.

Miserendino, M.J.D and Davis, M. NMDA and non-NMDA antagonists infused into the nucleus reticularis pontis caudalis depress the acoustic startle reflex. Brain Research, 1993, 623, 215-222.

Kim., M. and Davis, M. Lack of a temporal gradient of retrograde amnesia in rats with amygdala lesions assessed with the fear-potentiated startle paradigm. Behavioral Neuroscience, 1993, 107, 1088-1092.

Grillon, C., Falls, W.A., Rezvan, A., and Davis, M. Safety signals and human anxiety: A Fear-potentiated startle study. Anxiety, 1994, 1, 13-21.

Grillon, C., Ameli, R,. Goddard, A., Woods, S.W.and Davis, M. Baseline and fear-potentiated startle in panic disorder patients. Journal of Biological Psychiatry, 1994, 35, 431-439.

Liang, K.C., Hon, W., and Davis, M. Pre- and post-training intra-amygdala infusions of N-methyl-d-aspartate receptor antagonists impair memory in an inhibitory avoidance task. Behavioral Neuroscience, 1994, 108, 241-253.

Davis, M., Hitchcock, J.M., Bowers, M.B., Berridge, C.W., Melia, K.R., and Roth, R. H. Stress induced activation of prefrontal cortex dopamine turnover: Blockade by lesions of the amygdala. Brain Research, 1994, 664, 207-210.

Falls, W. A. and Davis, M. Fear-potentiated startle using three conditioned stimulus modalities. Animal Learning and Behavior, 1994, 22, 379-383.

Lee, Y., Schulkin, J. and Davis, M. Effect of corticosterone on the enhancement of the acoustic startle reflex by corticotropin releasing factor. Brain Research, 1994, 666, 93-98.

Grillon, C. and Davis, M. Effect of anticipatory anxiety induced by the threat of shock on prepulse inhibition. Psychophysiology, 1994, 31, 53-55.

Campeau, S. and Davis, M. Involvement of the central nucleus and basolateral complex of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. Journal of Neuroscience, 1995, 15, 2301-2311.

Campeau, S. and Davis, M. Involvement of subcortical and cortical lateral amygdala afferents in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. Journal of Neuroscience, 1995, 15, 2312-2327.

Campeau, S. and Davis, M. Prepulse inhibition of the acoustic startle reflex using visual and auditory prepulses: Disruption by apomorphine. Psychopharmacology, 1995, 117, 267-274.

Falls, W. A. and Davis, M. Lesions of the central nucleus of the amygdala block conditioned excitation, but not conditioned inhibition of fear as measured with the fear-potentiated startle effect Behavioral Neuroscience, 1995, 109, 379-387.

Gewirtz, J.C. and Davis, M. Habituation of prepulse inhibition of the startle reflex using a weak auditory prepulse. Behavioral Neuroscience, 1995, 109, 388-395

deLima, T. C. M. and Davis, M. Involvement of cyclic AMP at the level of the nucleus reticularis pontis caudalis in the acoustic startle reflex. Brain Research, 1995, 700, 59-69

Morgan, C. A., Grillon, C., Southwick, S. M., Southwick, S. M., Davis, M., and Charney, D.S. Fear-potentiated startle in posttraumatic stress disorder, Biological Psychatry, 1995, 38, 378-385.

Morgan, C. A., Grillon, C., Southwick, S. M., Southwick, S. M.,Nagy, L.M., Davis, M., Krystal, J. H. and Charney, D.S. Yohimbine facilitated acoustic startle in combat veterans with posttraumatic stress disorder, Psychopharmacology, 1995, 117, 466-471.

Grillon, C. and Davis, M. Acoustic startle and anticipatory anxiety in humans: Effects of monaural right and left ear stimulation, Psychophysiology, 1995, 32, 155-161

Reviews and chapters

Davis, M. Neural substrates of classical conditioning: The fear-potentiated paradigm. In: The Encyclopedia of Learning and Memory (Larry Squire, Ed.). MacMillan publishing Co.: New York, 1992, pp. 480-483.

Davis, M. and Egger, M.D. Habituation and sensitization in vertebrates: Behavioral properties and neural substrates. In: The Encyclopedia of Learning and Memory (Larry Squire, Ed.). MacMillan publishing Co.: New York, 1992, pp. 237-241

Charney, D.S., Deutch, A Y., Krystal, J.H., Southwick, S.M. and Davis, M. Psychobiological mechanisms of post-traumatic stress disorder. Archives of General Psychiatry, 1993, 50, 294-305.

Davis, M. Pharmacological analysis of fear-potentiated startle. Brazilian Journal of Medical and Biological Research, 1993, 26, 235-260.

Davis, M., Falls, W.A., Campeau, S. and Kim, M. Fear-potentiated startle: A neural and pharmacological analysis. Behavioural Brain Research, 1993, 58, 175-178.

Bremner, J.D., Davis, M., Southwick, S.M., Krystal, J.H., and Charney, D.S. Neurobiology of postraumatic stress disorder. In: Posttraumatic stress disorder: A clinical review. R.S. Pynoos (Ed), Sidran Press: Lutherville, Md., 1994, pp. 43-64.

Davis, M. The role of the amygdala in emotional learning. In: International Review of Neurobiology, 34, Academic Press: New York, 1994, pp. 255-266.

Davis, M. Rainnie, D. and Cassell, M. Neurotransmission in the rat amygdala related to fear and anxiety. Trends in Neuroscience, 1994, 17, 208-214.

Davis, M., Campeau, S., Kim, M. and Falls, W.A. Neural systems of emotion: The amygdala's role in fear and anxiety. In: Brain and Memory: Modulation and Mediation of Neuroplasticity, (J. McGaugh,N.M. Weinberger, and G.

Lynch, Eds), Oxford University Press: New York, 1995, pp. 3-40.

Morris, R. G. M. and Davis, M. The role of NMDA receptors in learning and memory, (Second Edition). In: The NMDA Receptor, (J.C. Watkins and G.L. Collingridge, Eds), Oxford University Press: Oxford, 1994, pp. 340-375.